UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,550	12/09/2003	Ole Isacson	083883-0302	4567

30542 7590 01/31/2007

FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,550	ISACSON ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *2,7,14 and 17-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-13,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/04, 10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 10-31-06.

Claims 1-46 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group I, PTX-3, human cells and Smad 4, in the reply filed on 10-31-06 is acknowledged. The traversal is on the ground(s) that no undue burden will be placed on the Examiner in examining all of the Groups claimed because similarities exist between the different methods claimed, and the groups require searching in the same class and subclass. This is not found persuasive because the different methods claimed comprise different and distinct steps and the searching of one Group will not be coextensive with another Group, although the two may overlap, as evidenced by overlap in classification. Each of the methods claimed requires searching the prior art (NPL and patent literature), and includes addressing enablement and written description standards for each Group. Contrary to Applicant's assertions, the proper searches required for examination of each of the methods claimed would pose an undue burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2, 7, 14, 17-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10-31-06.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 8-13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods for generating dopaminergic neurons in vitro or in vivo comprising inhibiting one or more pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing one or more cell fate-inducing polypeptides in the target pluripotent cells.

The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the broad genera claimed, comprising *pathway components of a TGF-β signaling pathway* or *cell fate-inducing polypeptides*, whereby manipulating expression of these molecules provides for the generation of dopaminergic neurons in any target pluripotent cells, e.g. upon inhibition of any TGF-β signaling pathway component and overexpression of any cell fate-inducing polypeptide.

The instant disclosure teaches gene expression profiles of in vitro differentiation of (previously generated) Smad4 -/- and Cripto -/- mouse embryonic stem cells (ESC)

using a five-stage differentiation protocol. The observation of increased expression of mesencephalic dopaminergic markers (e.g. Nurr-1) during later stages of in vitro differentiation of Smad4 -/- and Cripto -/- ES cells, and the known availability from previous investigators of cell lines which overexpress some cell fate inducing genes, however, do not provide adequate written description for the broad genera of molecules claimed.

The specification and claims do not adequately teach a representative number of species for the very broad genera of TGF-β signaling pathway components or cell fate-inducing polypeptides, that, upon inhibition or overexpression respectively, provide for the generation of dopaminergic neurons in any pluripotent target cell in vitro or in vivo. Concise structural features that could distinguish compounds within these broad genera from others are missing from the disclosure, whereby a representative number of species of each genus is disclosed, and which provide for the functions claimed, of providing dopaminergic neurons in any pluripotent target cell in vitro or in vivo upon alteration of expression. One of skill would reasonably conclude the instant invention lacks adequate written description for the broad genera of molecules providing for the methods claimed.

Claims 1, 3-6, 8-13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating gene expression profiles of in vitro differentiation of (previously generated) Smad4 -/- and Cripto -/- mouse embryonic stem cells (ESC) using a five-stage differentiation protocol, and for

transplantation of Smad4 -/- and Cripto -/- grafts in mice in vivo, whereby expression of neuron associated genes in these grafts were not statistically significant compared to WT grafts, does not reasonably provide enablement for methods for generating dopaminergic neurons in vitro or in vivo comprising inhibiting one or more pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing one or more cell fate-inducing polypeptides in the target pluripotent cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods for generating dopaminergic neurons in vitro or in vivo comprising inhibiting one or more pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing one or more cell fate-inducing polypeptides in the target pluripotent cells.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene therapy and stem cell development in organisms.

Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo

inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50; *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches. Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of effector compounds, including nucleic acids, by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy...." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of nucleic acids in sufficient amounts to effect a phenotype or desired effect in vitro and in vivo (see Agrawal et al especially at pages

79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic nucleic acids to target cells).

See also the discussion by Opalinska et al of unpredictability of nucleic acid therapy, including the use of siRNA and antisense in vivo (Opalinska et al, Nature Rev., 1: 503-514, at 503 and 511). "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain... The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field. ...it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability." [references omitted].

Zwaka et al (Nature Biotech., Adv. Online Publ, pp. 1-3, Feb. 10, 2003, provided in the IDS filed 5-21-04) teach that significant differences exist between different embryonic stem cells (e.g. mouse vs. human) and that high, stable transfection efficiencies in human ES cells are difficult to achieve. Zwaka also teach that protocols established for mouse ES cells work poorly in human ES cells (see abstract). In addition, Odorico et al (Stem Cell, Vol. 19, pp. 193-204, 2001, provided in the IDS filed 5-21-04) point out many barriers that remain in successfully employing the transplantation of human ES cells or human-derived ES cells in the clinic. Odorico also

details the differences that exist between human and mouse ES cells, as well as differences in vitro culture requirements for maintaining different sources of ES cells (see esp. pp. 194-195).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided sufficient guidance in the specification toward a method of generating dopaminergic neurons in vitro or in vivo in any ES cells (including human) comprising inhibiting any pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing any cell fate-inducing polypeptides in the target pluripotent cells

The instant disclosure teaches gene expression profiles of in vitro differentiation of (previously generated) Smad4 -/- and Cripto -/- mouse embryonic stem cells (ESC) using a five stage differentiation protocol, as well as the increased expression of mesencephalic dopaminergic markers (e.g. Nurr-1) during later stages of in vitro differentiation of Smad4 -/- and Cripto -/- ES cells. The specification also teaches the general availability from previous investigators of cell lines which overexpress some cell fate inducing genes. The specification teaches the transplantation of Smad4 -/- and Cripto -/- grafts in mice in vivo, whereby expression of neuron associated genes in these grafts was not statistically significant compared to wild type grafts

These teachings are not representative or correlative of the ability to generate dopaminergic neurons in vitro or in vivo comprising inhibiting one or more pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing one or more cell fate-inducing polypeptides in the target pluripotent

cells. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and the subsequent inhibition of any TGF-β signaling pathway component or overexpression of any cell fate inducing gene, whereby dopaminergic neurons are generated in vitro or in vivo. The specification as filed fails to provide the specific guidance necessary for the skilled artisan to carry out the entire protocol with any predictable degree of success.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to methods for generating dopaminergic neurons in vitro or in vivo comprising inhibiting one or more pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing one or more cell fate-inducing polypeptides in the target pluripotent cells. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues whereby dopaminergic neurons are generated in vitro or in vivo following administration of a sufficient number of representative species of pluripotent target cells comprising altered expression of the broad genera of molecules claimed, and which are appropriately inhibited or overexpressed. Since the specification fails to provide sufficient guidance for the generation of dopaminergic neurons using any of the methods claimed, it would require undue experimentation to practice the invention over the broad scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
1-17-07

J Zara
TC 1600

JANE ZARA, PH.D.
PRIMARY EXAMINER